Commentary

Lead Poisoning—One Approach to a Problem That Won't Go Away

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A reduction in sources of environmental lead exposure has resulted in substantial declines in mean blood lead concentrations of all age groups in the United States. However, some segments of the population continue to have unacceptable levels of lead exposure and elevated blood lead concentrations. In addition, virtually all residents of industrialized countries have bone lead stores that are several orders of magnitude greater than those of our preindustrial ancestors. Recent studies suggest that these skeletal lead stores adversely affect health and can contribute to reduced birth weights, aggressive behavior in children, and anemia, hypertension, and kidney disease in adults. Evidence is described that demonstrates that an increase in dietary calcium consumption can reduce lead absorption and toxicity from exogenous and endogenous lead exposure. A relatively inexpensive and effective way to reduce the substantial morbidity that will result from widespread lead exposure is by fortification of a variety of foods with low levels of calcium. This approach can complement other efforts to prevent lead exposure and reduce lead toxicity. *Key words*: bone, calcium, food, lead, toxicity.
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Elimination of the use of lead in gasoline in the 1970s and reduced use of lead in other sources of exposure such as outdoor paint, printing inks, and solder in tin cans used for food have resulted in well-documented and substantial decreases in blood lead concentrations of U.S. residents (*1,2*). Despite these efforts, young children, especially those living in urban areas, have been and continue to be exposed to excessive amounts of lead from paint chips, soil, and various other sources. The substantial short-term toxic manifestations of lead exposure during childhood are well known (*3*). What has not been fully appreciated is that moderate lead exposure during early childhood can lead to further consequences during late childhood, pregnancy, lactation, and even late in life, and that bone lead stores can serve as a significant internal source of lead exposure throughout life.

Lead Toxicity and Bone Lead

Because of the persistence of lead in various environmental sources and its long skeletal half life, approximately 20 years or more for cortical bone (*4*), skeletal lead concentrations increase inevitably with age. For example, mean tibia lead concentrations (micrograms per gram ash) have been estimated to be about 3 µg/g for teenagers, 17 µg/g for adults 35–50 years of age, and 30 µg/g for older adults above age 75 (*5*). The increase with age is probably due both to the long skeletal half-life and higher environmental exposures in the past. In fact, age alone accounts for about half the variability in bone lead concentrations (*6*).

It has been hypothesized that the high rate of bone remodeling during childhood, and the consequent high calcium and lead turnover, results in a substantial reduction in bone lead stores so that much of the lead incorporated into bone during childhood does not persist into adulthood (*7*). However, a recent experimental study (*8*) suggests that extensive turnover in the skeleton cannot overcome the greater absorption of lead that occurs in young animals. In this investigation we compared bone lead accumulation in young (5–10 weeks old), teenage (10–15 weeks old), and adult rats (15–20 weeks old) given lead in their drinking water for 5 weeks and found that femur lead concentrations 1 month after cessation of lead exposure were 2.7- and 4.4-fold higher in the young rats than in the teenage or adult rats, respectively. Vertebrae lead concentrations followed a similar pattern. Even after an additional 4 months, the young rats continued to have the highest bone lead concentrations. These data demonstrate that exposure at a young age can lead to substantial skeletal lead accumulation and retention despite a high rate of bone remodeling. Based on studies in humans, Kosnett et al. (*6*) suggest that even by the end of the sixth decade of life, more than one-third of the skeletal mass is composed of unremodeled bone acquired during childhood and adolescence. Thus, a substantial fraction of the lead incorporated into bone at a young age will remain there for many years.

Patterson et al. (*9*) have compared current skeletal lead concentrations with those of Southwest American Indians who lived 700–1,000 years ago by use of museum samples. They found that the present concentrations are about 500- to 1,000-fold greater than those of the museum samples, suggesting that current body lead burdens are about three orders of magnitude greater than those of our preindustrial ancestors. Thus, it should not be surprising that adverse health effects have been associated with modestly increased bone lead stores in recent studies, including diminished academic achievement and aggressive behavior in children, and anemia, high blood pressure, and compromised renal function in adults (*10–13*).

Because lead is a ubiquitous and widespread contaminant, it will not be possible to eliminate additional environmental exposure of Americans of all ages. This inevitable exogenous exposure will be augmented by endogenous exposure as a result of past and ongoing bone lead accumulation.

Dietary Calcium and Lead

In the last 25 years, the blood lead concentration used to define poisoning or excessive exposure has fallen progressively from 40 to 30 to 25, and finally to 10 µg/dl (*3*). Children with concentrations of 45 µg/dl or greater are treated with chelation therapy. Even though concentrations from 10 to 44 µg/dl are indications of excessive exposure and toxic effects, children with concentrations in this range are generally not treated with drugs (*3*). Instead the recommendation is to eliminate any additional lead exposure. In part, these guidelines are based on the realization that chelation treatment with standard drugs such as calcium disodium versenate and D-penicillamine carries a substantial risk of adverse effects (*3*). In particular, these chelating agents are nonspecific, binding and promoting the excretion not only of lead but also of essential metals such as zinc and copper. They have other adverse effects, including the potential for considerable nephrotoxicity. The current guideline of nontreatment would be inappropriate if safe treatments were available. Two approaches may allow a more suitable recommendation. One is the potential availability of a relatively safe oral

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chelating agent (succimer) now being tested in children with blood lead concentrations of 20–44 µg/dl. The other is a simple dietary manipulation, an increase in dietary calcium ingestion, that can prevent and even reverse accumulation of lead in critical tissues and body reservoirs.

It has been known for more than 50 years that an increase in dietary calcium in experimental animals will decrease gastrointestinal lead absorption and retention, an effect likely mediated in large part by relationships among lead absorption and excretion, dietary calcium, and vitamin D metabolism (*14,15*). In rats, an increase in dietary calcium can reduce bone lead accumulation and its mobilization during pregnancy and lactation, and probably at other times (*16,17*). Blood lead concentrations have been reported to be lower in 1–11-year-old children who have relatively high dietary calcium intakes (1,100 mg/day at the 75th percentile vs. 522 mg/day of calcium at the 25th percentile) than in those children who consume less calcium (*18*). Ziegler et al. (*19*) found that calcium intake was inversely associated with lead retention in infants and that negative lead balances were more likely to be found in those infants with relatively high calcium ingestion, including intakes as high as 160–180 mg/kg/day (1,600–1,800 mg/day calcium for an infant who weighs 10 kg). Recent studies done in Mexico (*20,21*) have found that pregnant or lactating postpartum women with relatively high dietary calcium intakes have lower blood or bone (patella or tibia) lead concentrations. Although there were some dose-related inconsistencies in the lead–calcium relationships reported, these are probably due to the difficulty of accurately assessing calcium intakes. Thus, there are sufficient data to suggest that an increase in dietary calcium could be very effective in reducing lead absorption and toxicity.

An increase in dietary calcium obviously cannot correct any irreversible damage to the central nervous system or other organs caused by past lead ingestion or inhalation, but it can help prevent adverse effects from additional exogenous and continuous endogenous lead exposure. One potential consequence of this lead exposure is an increase in blood pressure during pregnancy. A recent meta-analysis (*22*) of the relationships among calcium supplementation, pregnancy-induced hypertension, and preeclampsia analyzed data from 14 randomized trials involving 2,459 women. The authors concluded that calcium supplementation during pregnancy leads to significant reductions in systolic and diastolic blood pressure as well as the incidence of preeclampsia. However, the mechanism(s) for this effect is unknown, but it could be due to calcium–lead interactions. We have found that rats exposed to lead during pregnancy (*16*) or prior to pregnancy (*17*) and fed diets low in calcium during pregnancy have higher blood pressures than both non-lead-exposed rats and lead-exposed rats given adequate dietary calcium. Thus, it is possible that the beneficial effects of calcium on blood pressure during pregnancy may be due in part to its interactions with lead and that increased calcium intakes can reduce lead mobilization from the skeletons of pregnant women; studies are required to further investigate this possibility. In addition, a reduction of *in utero* lead exposure by increasing calcium intake can provide short- and long-term benefits for the fetus, including an increase in birth weight (*16*).

The 1997 dietary reference intakes (DRIs) for calcium are 800–1,300 mg/day for the various age and gender subgroups above 3 years of age (*23*). A 1994 NIH consensus statement (*24*) on dietary calcium recommends intakes for some age and gender subgroups (up to 1,500 mg/day) that are even higher; both the latter and the new DRIs are substantially higher than current calcium consumption (500–700 mg/day) of adults (*23*). Besides the projected beneficial effects of these increased intakes on bone mass and the incidence of osteoporosis, a generally unrecognized additional benefit will be reductions in gastrointestinal lead absorption and bone lead accumulation and retention. Publicizing and implementing the new DRIs for calcium could have a major beneficial health impact on the millions of American children and adults who have been excessively exposed to lead. Indeed, it could be persuasively argued that all of us have had excessive lead exposures. In our laboratories we have measured more than 130,000 blood lead concentrations and have not yet found anyone with an undetectable level. In fact, as Patterson and Settle (*25*) have noted, it is not possible to find unexposed people, so comparison of those with excessive exposure to controls may underestimate the toxic effects of lead.

Unfortunately, dietary intakes of calcium for most Americans fall well below the DRIs and NIH consensus statement guidelines. This is particularly true for African-American children and adults (*26*), who are also more likely to have been exposed to excessive amounts of lead than Caucasians. For example, median dietary calcium intakes for 1–2-year-old children were found to be 817 mg/day for non-Hispanic white children but only 656 mg/day for black children. Corresponding median intakes for 3–5 year olds were 822 mg/day for white children and 670 mg/day for their black counterparts. For young women of childbearing age (20–29 years old), the median intake for whites was a relatively low 647 mg/day, but was only 582 mg/day for young black women. A comprehensive program to increase dietary calcium to the DRI guidelines in all age groups could help reduce the enormous toxic potential of the massive amounts of lead that have been so carelessly released into the environment.

Current intakes of calcium are not adequate to build or maintain optimal bone mass; however, it could be argued that they are already high enough to have a maximum beneficial effect on lead absorption and toxicity. Both animal and human studies suggest, in fact, that current intakes are not high enough to achieve the latter objective.

Studies in rats demonstrate more substantial increases in lead absorption and toxicity in rats fed diets containing 1 mg/g than in those fed 5–7 mg/g of calcium in their food (*15,16,27*). Assuming ingestion of 15 g food daily by a rat weighing 400 g, a diet containing 1 mg/g is equivalent to a daily dose of calcium of 37.5 mg/kg, but is not sufficient in the rat to prevent substantial lead accumulation and toxicity when compared to a five- to sevenfold higher intake. Even the highest calcium intake recommended in the NIH consensus statement (1,500 mg/day) is only a daily dose of 25 mg/kg for a woman weighing 60 kg. If the rat data are applicable to humans, the beneficial effects of calcium on lead absorption and toxicity are not limited to relatively modest increases in calcium intake, but in fact will occur at intakes up to and even well above 1,500 mg/day.

Studies in humans also suggest that, within the range of typical dietary calcium intakes, higher intakes are associated with lower blood lead concentrations for several age/gender groups including infants and children (*18,19*), pregnant women (*20,21*), and older women (*28*). For example, in the study of children (*18*), the 25th, 50th, and 75th percentiles of calcium intake were 522, 789, and 1,100 mg/day, respectively, suggesting that relatively high intakes can further reduce lead absorption and toxicity compared to low and moderate intakes. In the study of infants (*19*), intakes up to 160–180 mg/kg/day (about 1,600–1,800 mg/day for a 10-kg child) were associated with reduced lead retention in comparison to intakes of 60–120 mg/kg/day (600–1,200 mg/day for a 10-kg child). The study of 530 older women is particularly noteworthy (*28*). Women in this study in the highest two quartiles of calcium ingestion (1,039–1,642 mg/day and >1,642 mg/day) had significantly lower blood lead concentrations than those in the lowest quartile of calcium ingestion (<623 mg/day). The

lowest blood lead concentrations occurred in the women ingesting >1,642 mg/day. Some women in this study achieved their relatively high intakes by ingestion of calcium supplements. Thus, the human studies suggest that dietary calcium intakes well above current levels will reduce lead absorption and toxicity over a broad age range.

An increase in dietary calcium may have some potential drawbacks. Calcium is known to decrease iron and zinc absorption (*29–31*) so it will be important to include adequate amounts of these key nutrients in our diets, especially since they may also reduce gastrointestinal lead absorption (*32,33*). In addition, although the calcium present in milk and other dairy products may well decrease lead absorption and toxicity, this benefit may be reduced to some extent by the lactose in dairy foods; lactose has been reported to increase the absorption of divalent metals, including lead (*34,35*). Another concern is that an increase in dietary calcium may enhance hypercalciuria and promote the development of kidney stones. However, studies in rats (*15,36*) and a prospective epidemiologic investigation (*37*) demonstrate that an increase in dietary calcium paradoxically reduces the development of calcium-containing kidney stones. The mechanism is likely to be suppression by dietary calcium of phosphate and oxalate absorption in the gut, thereby reducing the exposure of the kidney to the anions needed for stone formation. In a recent review, Whiting and Wood (*38*) conclude that it is unclear whether chronic doses of calcium greater than 2,000 mg/day will have a negative or positive effect on stone formation. Intakes consistently above this level may be detrimental and we do not recommend them.

However, these potential limitations are modest in comparison to the substantial benefits that will result from an increase in the consumption of milk and other sources of calcium in the diets of both children and adults. Heaney (*39*) has recently emphasized that a low calcium intake is an excellent marker for a diet that is low in other key nutrients. He notes that per capita milk consumption has declined annually for about 20 years, thereby leaving a "polynutrient hole" in the diet of U.S. residents. His suggestion to use low-level fortification of a variety of nutritionally sound foods with calcium will not only solve a key nutrition problem, but it will also reduce lead-related morbidity. An advantage of fortifying nondairy foods with calcium is that the absence of lactose in such foods may allow the calcium to more effectively reduce lead absorption and toxicity. This approach will probably be more efficient and safer than recommending the widespread use of calcium supplements by millions of children and adults, though pediatricians and other health practitioners may want to prescribe the use of supplements for individual patients whose diets are inadequate in calcium and who are resistant to making changes that will increase their calcium intake from foods. Despite the widespread availability of calcium supplements, many individuals with low calcium intakes will probably not purchase and use supplements without encouragement from their physicians. We must ensure that such products do not contain excessive lead, as has been reported for some kinds of calcium supplements (*40*).

It is beyond the scope of this brief commentary to attempt a cost/benefit analysis of the impact of increasing dietary calcium on lead toxicity. Clearly, the costs of lead toxicity are enormous. They include treating asymptomatic and symptomatic lead poisoning in young children; lower IQs for a significant percent of the population; possible contributions to aggressive and delinquent behavior in young males, as identified in recent publications; and anemia, hypertension, and kidney disease in adults (*10–13*). A possibility is that the predisposition of African Americans to develop high blood pressure (*41*) may be potentiated by the combination of lead exposure and low dietary calcium. These economic and social costs are no doubt very large in comparison to the costs that would be expended for a national program to increase dietary calcium intake. Furthermore, the benefits would include not only a reduction in lead toxicity but a decrease in the incidence of osteoporosis in women, especially if increased dietary calcium intake began at an early age.

Conclusion

There is an obvious but important lesson to be learned from our past collective failure to appreciate the enormous health problems posed by lead. Widespread contamination of the environment with a toxin known to have major adverse consequences will inevitably result in substantial human exposure and toxicity. Furthermore, we will identify previously unknown health effects when looked for in carefully designed studies. Lead is of particular concern because it is both persistent in the environment and has a long biological half-life.

The major source of environmental lead exposure is paint and paint dust in homes. In fact, the U.S. Department of Housing and Urban Development estimates that three-fourths of homes built before 1978 contain lead-based paint (*42*). It is a formidable but important task to reduce exposure from this key source; however, it will take considerable time to properly abate the lead in millions of housing units. Our recommendation to increase dietary calcium intakes is not an alternative to such efforts to reduce lead exposure from paint and other sources, but rather an additional approach to be used in conjunction with other preventive strategies.

A recent study (*43*) of more than 20,000 adults provides data which show that, despite attempts to promote increased consumption of dairy foods, the calcium intake of the U.S. population decreased by 5.1% between 1987 and 1992. Thus, we are unlikely to achieve intakes that approach the 1997 DRIs without food fortification.

It could be argued that more studies, including dose–response studies, are needed before fortification of a variety of foods with calcium can be recommended as a means to reduce lead toxicity. It is true that we do not know the ideal amount of dietary calcium to achieve this objective. However, the available evidence demonstrates that any increase in dietary calcium up to and above the new DRIs or NIH consensus statement levels will reduce lead absorption and toxicity, as previously discussed. The amounts of calcium in fortified foods should be based on the DRIs that are set to maximize bone health; the effects on lead will be an additional benefit. Delaying the implementation of a strategy of increasing dietary calcium intakes would be unwise since millions of people would continue to suffer unnecessarily from the adverse effects of lead while waiting for the results of studies to fine-tune the dietary calcium intakes that most efficiently reduce lead toxicity in males and females of various ages.

The Centers for Disease Control's "Strategic Plan for the Elimination of Childhood Lead Poisoning" (*44*) focuses on removal of leaded paint and abatement of paint-contaminated dust in high risk housing, continued reduction of other sources of exposure for children, a national program for surveillance by measurement of blood lead concentrations, and various childhood lead poisoning prevention programs and activities. These are worthwhile goals. However, this detailed report only briefly suggests the importance of nutrition. A much stronger emphasis on nutritional factors, in particular an increase in dietary calcium for both children and adults, is warranted. The best way to do this is by fortification of a variety of foods with calcium.

The ability of increases in dietary calcium to reduce lead toxicity was first identified more than 50 years ago (*45*). Effective use of this knowledge to help prevent the serious consequences of lead exposure is long overdue.

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